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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,744	01/05/2004	Mark A. Schenerman	AE300US1	6583
36577 7590 08/31/2007 JOHNATHAN KLEIN-EVANS ONE MEDIMMUNE WAY GAITHERSBURG, MD 20878				
			EXAMINER ZEMAN, ROBERT A	
			ART UNIT 1645	PAPER NUMBER
			MAIL DATE 08/31/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/751,744

Applicant(s)

SCHENERMAN ET AL.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
- 4a) Of the above claim(s) 10-18 and 27-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 19-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION***Election/Restrictions***

Applicant's election with traverse of Group I in the reply filed on 2-28-2006 is acknowledged. The traversal is on the ground(s) that Groups I and III should be examined together as the search and examination of both groups would not entail a "serious burden". A search of nucleic acid claims would provide useful information for examining claims directed to both nucleic acids and the IgG polypeptides encoded by these nucleic acids and most publications include the deduced amino acid sequence of the encoded polypeptide when disclosing nucleic acid sequences. This is not found persuasive because polypeptides and polynucleotides are chemically distinct products, since polypeptides are composed of polymers of amino acids, whereas polynucleotides are composed of polymers of nucleotides. Any relationship between a polynucleotide and a polypeptide is dependent upon the information provided by the nucleotide sequence of the polynucleotide, as it corresponds to an "open reading frame" encoding the amino acid sequence of the polypeptide. However, a polypeptide can be produced by means, other than the recombinant means by which a polynucleotide encoding a polypeptide might be used to produce the polypeptide, since a polypeptide can be produced (or isolated) by biochemical means, including, for example, affinity chromatography. In addition, while the polynucleotide might encode the polypeptide, generally, it can also encode another polypeptide using the information provided by an alternative open reading frame; and furthermore, since a polynucleotide can be used as a probe in hybridization-based analyses, the information provided by a polynucleotide can be used to isolate different polynucleotides encoding polypeptides, which have amino acid sequences that differ from the amino acid sequence

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encoded by the disclosed polynucleotide. Consequently, the disclosed relationship between a polynucleotide capable of encoding a polypeptide and the polypeptide is not exclusive, since either the claimed polynucleotide or the claimed polypeptide can also be related to other polynucleotides or polypeptides, which are materially and chemically different from the claimed inventions.

The invention of Group I and the invention of Group III have acquired a separate status in the art, as evidenced by their different classifications, and the search performed in examining claims drawn to a polynucleotide is different from the search performed in examining claims drawn to a polypeptide. Apart from the searching patent databases using the patent classification of the claimed subject matter, a thorough search of the technical literature is particularly pertinent, and since such a search is performed by a series of key word queries of relevant databases, each search would be performed using a different set or series of key words. Therefore, the search and considerations necessary in examining the merit of claims directed to the inventions of Group I would not suffice to provide adequate information regarding the merit of the claims directed to the invention of Group III, and vice versa, since the searches are not coextensive in scope and nature. Because different searches would have to be performed to examine the invention of Group I and the invention of Group III, an examination of both would constitute a serious burden. Moreover, because the disclosed relationship between the polynucleotide and the polypeptide encoded by the polynucleotide is not absolute or exclusive of other relationships with different polynucleotides or polypeptides, the search of either group will likely provide information that is relevant to one but not the other; and as such, searching one in addition to the other would be unduly burdensome.

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Finally, since the invention of Group I and the invention of Group III are patentably distinct from the other and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-42 are pending. Claims 10-18 and 27-42 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-9 and 19-26 are currently under examination.

Specification

The use of the trademarks SYNAGIS® has been noted in this application (see page 5 for example). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It should be noted that the cited occurrences of improper use are only exemplary and Applicant should review the entire specification to correct any other improper use of trademarks.

Claim Objections

Claims 22-26 are objected to because of the following informalities: said claims recite the acronym HPSEC without defining it upon its first recitation. Appropriate correction is required.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1-9 and 19-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) still contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to modified IgG molecules comprising a modified hinge region comprising one or more amino acid modifications at a position corresponding to positions 233 to 239 of human IgG1 and/or an amino acid modification at a residue corresponding to position 249 of a human IgG1 heavy chain wherein said modified IgG exhibits reduced degradation upon heating to 55°C for one week compared to an unmodified IgG and pharmaceutical compositions comprising said modified IgG molecules.

The claims are drawn to a vast genus of modified immunoglobulins containing one or more mutations to positions 233 to 239 of an undefined hinge region of a human IgG1 and/or an mutation to position 249 of a human IgG1 heavy chain wherein said mutations confer an

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resistance to heat degradation. Consequently, since the instant claims recite specific "residues", it is deemed that the baseline IgG sequences constitute essential material. The MPEP states:

608.01(p)

Newly filed applications obviously failing to disclose an invention with the clarity required are discussed in MPEP § 702.01. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below.

"Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material **may not be** incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of the aforementioned modified immunoglobulins, Applicant must adequately describe the specific mutations that would lead to the desired increase in heat resistance.

However, the specification does not disclose distinguishing and identifying features of a

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representative number of members of the genus of modified immunoglobulins to which the claims are drawn, such as a correlation between the structure of the immunoglobulin and its recited function (increased resistance to heat), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acids might be deleted or replaced so that the resultant immunoglobulins possess the desired characteristics. The specification is equally silent with regard to which additional amino acids can be inserted so that the resultant immunoglobulin possesses the desired characteristic. Therefore, since the specification fails to adequately describe at least a substantial number of mutations that would convey an increased resistance to degradation by heat, the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunoglobulins possessing the desired characteristics.

MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See

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Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species

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within the genus. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoglobulins**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining or altering a function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of modified immunoglobulins, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of modified immunoglobulins with increased resistance to degradation by heat. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of mutations conferring increased resistance to heat degradation is not deemed representative of the genus of modified immunoglobulins to which the claims refer.

Enablement Rejection

Claims 1-9 and 19-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to

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comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a vast genus of modified immunoglobulins containing one or more mutations to positions 233 to 239 of an undefined hinge region of a human IgG1 and/or an mutation to position 249 of a human IgG1 heavy chain wherein said mutations confer an resistance to heat degradation. However, Applicant has failed to provide sequences on which the claimed mutations are based. Consequently, the skilled artisan cannot make and use the claimed invention. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoglobulins**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining or altering a function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306) Therefore, given the lack of sequences on which the claimed mutations are based, the lack of success in the art, the lack of

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working examples commensurate in scope to the claimed invention and the unpredictability of the effects of a given mutation, the specification, as filed, does not provide enablement for the claimed modified immunoglobulins.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the use of the phrase "corresponding to position 233 to position of human IgG1 relative to a corresponding wild-type hinge region..."

It is unclear what is meant by the term "corresponding" or the term "relative". What is the basis of said correspondence? As written, it is impossible to determine the metes and bounds of the claimed invention. It is suggested that applicant recite the aforementioned limitation in terms of a specific sequence (i.e. SEQ ID NO).

Claim 1 is rendered vague and indefinite by the use of the phrase "corresponding to position 249 of human IgG1 heavy chain..."

It is unclear what is meant by the term "corresponding". What is the basis of said correspondence? As written, it is impossible to determine the metes and bounds of the claimed invention. It is suggested that applicant recite the aforementioned limitation in terms of a specific sequence (i.e. SEQ ID NO).

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Claim 5 recites the limitation "corresponding to position 237 of a human IgG1 heavy chain" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

The parent claim only recites position 249 of a human IgG1 heavy chain.

Claim 19 is rendered vague and indefinite by the use of the phrase "of any of claim 1". It is unclear what is meant by said phrase, as there is only one claim 1.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866.

The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system.

Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "Robert A. Zeman". The signature is fluid and cursive, with the first name "Robert" and last name "Zeman" clearly distinguishable.

ROBERT A. ZEMAN
PRIMARY EXAMINER

August 28, 2007